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Editorial Open Access

Melasma and Vitiligo: Novel and Experimental Therapies

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Editorial

Melasma and vitiligo are acquired disorders of pigmentation that, despite recent advances, present a therapeutic challenge. This is partly due to their complex pathogenesis. This article includes an evidence-based review of recent advances in the management of these diseases and highlights promising novel and experimental approaches.

Several factors are implicated in the pathogenesis of melasma, including genetic predisposition, ultraviolet radiation, thyroid disease, pregnancy, oral contraceptives, and drugs. The current approach to management incorporates a prevention strategy that includes sun avoidance, a broad spectrum sunscreen, discontinuation of oral contraceptives, avoidance of contact allergens and sensitizers, and minimization of heat and friction in the skin [1]. An intrauterine levonorgestrel-releasing device may be safer than oral contraceptives when melasma is concerned [2].

Topical medications are first-line treatment for melasma. A triple combination cream containing 0.05% tretinoin, 4.0%, hydroquinone (HQ), and 0.01% fluocinolone acetonide is specifically used for moderate-to-severe melasma together with sun protection measures. This triple cream can be safely used for up to 24 weeks, with minimal risk of skin atrophy after 6 months of use [1]. Additionally, a plethora of adjunctive topical agents has emerged to assist in the treatment of melasma, including mequinol, azelaic acid, arbutin, Kojic acid, ascorbic acid, rucinol, resveratrol, N-acetyl glucosamine, niacinamide, dioic acid, 4-n-butylresorcinol, oligopeptides, and botanicals such as sylimarin, orchid extracts, and licorice extract [3,4]. Combining HQ with any of the above products can be more effective than using HQ alone. Nonetheless, the efficacy of most of these agents remains to be demonstrated in randomized controlled studies despite promising in vitro and animal data. Some of these compounds are contact sensitizers and/or have other adverse effects.

4-n-butylresorcinol, a derivative of resorcinol, and oligopeptides are novel tyrosinase inhibitors that have shown some promise in melasma treatment [3]. A statistically significant reduction in the melanin index on the treatment side was found in a randomized controlled split-face trial in 23 patients with melasma treated with liposome-encapsulated 4-n-butylresorcinol 0.1% cream [5]. In a laboratory study, octapeptides P16-18 outperformed HQ in inhibiting tyrosinase and decreasing melanin content [6]. Hantash and Jimenez carried out a split-face, double-blind, randomized and placebo controlled pilot study to evaluate the efficacy of an emulsion containing 0.01% decapeptide-12 (Lumixyl cream) that was applied twice daily in 5 patients with Fitzpatrick phototype IV and moderate, recalcitrant melasma [7]. All patients showed statistically significant improvement with minimal side effects.

Although many botanicals have been used in melasma [8], there have been only a few rigorously designed studies. Several plant extract and phytochemicals effectively lighten epidermal melasma and hyperpigmentation induced by UV exposure. Best results have been reported with Chinese herbs, orchid extracts, ellagic acid, embilica, licorice extract, mulberry extract, silymarin, and soybean extract. Orchid extracts and sylimarin contain flavonoids that have antioxidant properties. Side effects of botanicals include worsened hyperpigmentation in some patients. Botanical extracts may play an integrative role in the treatment of hyperpigmentation. Further studies integrating botanicals with standard therapies are needed. Oral antioxidants, such as procyanidin may be helpful in melasma. Procyanidin, an oral antioxidant made from the French Maritime pine has been used in melasma. Oral use improved melasma by 20% after 8 weeks in a randomized, controlled trial of 60 Philippino women [9].

Chemical peels are 2nd-line treatment, and should be combined with topical medications and sunscreen [1]. Epidermal melasma can improve with α-hydroxy acid, Jessner, or salicylic acid (oily skin) peels whereas dermal/mixed melasma has been traditionally treated with trichloracetic acid (TCA) 25-35% with or without Jessner solution. Tretinoin mask and Obagi blue are promising new peels for melasma [3]. A 10% tretinoin mask was applied for 1 hour, and the treatment was repeated at 3-week intervals in an Italian study that included 20 female pts with skin types II-V [10]. Skin reddening lasted 3 days and no patients developed vesicles, crusting or erosions. Moderate or marked improvement was noted in all patients including darker skin types, and there was no relapse at 1 year. The Obagi blue peel is composed of TCA with a blue peel base that contains glycerine, saponins and blue color base ensures a slow and uniform penetration of TCA [3]. In a split-face comparative study involving 18 Korean women with moderate-to-severe melasma, a 1550-nm fractional laser was as efficacious as a 15% TCA peel after 4 weeks of therapy but recurrence was observed at 12 weeks in the TCA peel group [11].

Tranexamic acid (TA) is a novel melasma treatment, and may be considered as 3rd-line therapy in countries that has been approved for this indication. TA decreases melanocyte tyrosinase activity by preventing the binding of plasminogen to keratinocytes, which results in reduction of prostaglandins and arachidonic acid, inflammatory mediators involved in melanogenesis [12]. Oral TA has been reported to lighten melasma in several studies. The usual dose is 250 mg 2-3 times daily. TA should be taken for at least 1 month, and duration of treatment is more important than dose. Topical TA is ineffective and can cause irritation [3]. Good results were obtained with intralesional TA, as shown in a study of 100 Korean women with melasma [13]. TA

has a good safety profile, is temperature stable, UV insensitive, and does not become easily oxidized [3], thus providing a promising therapeutic option.

Lasers have been tried with variable success; therefore, they can be considered as 4th-line treatment. Their use has been associated with adverse effects such as post-inflammatory hyperpigmentation/mottling, rebound hyperpigmentation (multiple subthreshold exposures), hypopigmentation ("confetti-like" or "guttate hypomelanosis-like"), and depigmentation among others. Q-switched Neodymium Yttrium Aluminum Garnet (Nd:YAG) is the most widely used laser for melasma (fluence<5 J/cm^2, spot size 6 mm, frequency 10 Hz) [3]. Five to 10 treatment sessions at 1 week intervals are required. A modification of the protocol ("laser toning") involving lower fluence (1.6-3.5 J/cm^2) has become increasingly popular because it has been effective in most studies [14]. However, like other lasers, it has been associated with adverse effects such as hypopigmentation, depigmentation, and rebound hyperpigmentation. The combination of intense pulsed light (IPL), targeting the epidermal component of melasma, with q-switched Nd:YAG laser targeting both epidermal and dermal components is a promising approach. It was recently tried in patients with skin types III/IV that had mixed melasma [15]. Three treatment sessions at monthly intervals were performed, and a significant reduction in pigmentation was noted.

Therapeutic modalities in vitiligo reflect different modes of action but treatment needs to be tailored to disease course and clinical presentation, thus necessitating a customized approach. Differentiating between the segmental and non-segmental forms is of utmost importance because therapeutic options and prognosis differ [16]. According to a global Consensus Conference, the term vitiligo encompasses all nonsegmental forms of vitiligo, including the acrofacial, mucosal, generalized, universal, mixed, and rare variants [17]. An assessment of personal and family history, skin phototype, disease duration, extent and activity, Koebner phenomenon, and quality of life is crucial to an effective management plan [16]. Topical steroids, calcineurin inhibitors (pimecrolimus, tacrolimus), and narrowband ultraviolet light B (NB-UVB) remain the mainstay of vitiligo treatment. Still, a personalized approach to therapy is often required, and patient has to be involved in the decision to "repigment", "depigment" or "camouflage".

There is moderate evidence for the use of topical steroids but adverse effects are a limiting factor to long-term use [18]. Intralesional steroid injection is a novel approach to vitiligo treatment. A series of 9 patients that were treated successfully with intralesional triamcinolone acetonide 3 mg/mL was recently reported [19]. All patients responded with 80-90% repigmentation, and most patients maintained repigmentation for years. This promising approach is worth trying in patients with localized disease but its efficacy needs to be validated by randomized controlled studies. Calcineurin inhibitors, especially tacrolimus, are an alternative to topical corticosteroids for those skin areas where potent topical corticosteroids are contraindicated, such as the face, neck, and intertriginous areas.

Phototherapy (narrowband UVB (NB-UVB) and psoralen and UVA (PUVA) is second-line treatment for vitiligo [16]. NB-UVB (311 nm) phototherapy is as effective as PUVA and with fewer adverse effects [20]. Recent in this field led to the development of handheld units for home treatment of early onset vitiligo. Furthermore, targeted UVB phototherapy devices, such as excimer lamps or lasers (308 nm peak) can be useful in localized vitiligo, especially on cosmetically important areas such as the face and neck. A review of randomized controlled trials shows that combination interventions are superior to NB-UVB monotherapy; for example, combining calcineurin inhibitors [18] or oral antioxidants, such as alpha lipoic acid, vitamins C and E [21], and *Polypodium leucotomos* [22] with NB-UVB yields better results than NB-UVB monotherapy. Combination of NB-UVB with laser modalities has provided promising results. Mean improvement scores were higher with fractional CO_2 laser therapy followed by NB-UVB than NB-UVB monotherapy [23]. Also, a triple combination treatment with fractional CO_2 laser plus topical betamethasone and NB-UVB can be effective in refractory vitiligo [24]. Treatment with CO_2 laser ablation followed by 5-fluorouracil application may be beneficial in acral vitiligo [25]. The above studies highlight an increasing interest in laser treatment of refractory vitiligo.

Dexamethasone minipulse therapy for 3-6 months can be beneficial in fast spreading vitiligo [26]. Nevertheless, in another study, oral minipulse of steroid had only an adjunct value to NB-UVB and PUVA and was not very effective by itself [27]. Oral Ginkgo biloba has been effective in limited spreading disease [28] but the data is limited. Tumor necrosis factor-α antagonists halt disease progression in patients with progressive vitiligo [29] but this has yet to be studied in clinical trials. Overall, no therapeutic modality provides a reliable way to restrict the spread of disease. In a recent study, combination of afemelanotide (analogue of α-melanocyte-stimulating hormone) implant and NB-UVB phototherapy resulted in superior and faster repigmentation than NB-UVB monotherapy in generalized vitiligo [30]. Fifty five patients with skin phototypes III to IV were treated for 6 months and subsequently followed for 6 months. The study also indicated that patients with lesions on the face and upper extremities, and potentially those with darker skin, may have a more rapid desponse to the combination therapy. This is a promising modality in generalized vitiligo; however, diffuse hyperpigmentation induced by afamelanotide may increase the visibility of lesions in fair-skinned individuals [31].

Surgical modalities are a third-line treatment for vitiligo. They are indicated for small areas in patients with stable disease for at least 1 year [16]. Absence of Koebner phenomenon is a prerequisite because surgical modalities such as suction blister grafts can precipitate new vitiligo at donor sites. The surgical modalities consist of tissue grafts (full-thickness, split-thickness, and suction-blister grafts) and cellular grafts (cultured melanocytes and non-cultured epidermal cellular grafts) [20]. Although repigmentation rates are better with tissue grafts, cellular grafts offer the advantages of treating large areas and better cosmetic results than the tissue grafts [16]. Autologous transplantation of melanocytes works best for focal and segmental vitiligo [18] and offers an excellent treatment option for difficult to treat locations. Because melanocyte stem cells reside in the outer rooth sheath of hair follicles, suspension of ORS cells have been transplanted onto vitiligo lesions offering a repigmentation of 65.7% of vitiligo areas [32]. Other authors used single-cell suspensions of plucked hair follicles [33]. Results of these studies demonstrate a therapeutic potential of using melanocyte stem cells in vitiligo [34].

Several other experimental approaches to vitiligo management have been published. Authors of an in-vitro study suggested that administration of low-dose interleukin-10, interleukin-4, β-endorphin and basic fibroblast growth factor offers a targeted therapy for vitiligo [35]. Along the same lines, other authors have proposed therapies targeting cytokine pathways such as interferon γ-axis for vitiligo. Vitiligo has responded to tofacitinib [36], a Janus kinase inhibitor. The above biologic therapies have yet to be supported by clinical studies.

Furthermore, a need for improvement in the quality of the methodology of randomized controlled trials has been emphasized [18]. Inclusion of long-term follow-up, patient-rated outcomes, and health-related quality of life measures in randomized controlled trials will help to better evaluate existing and novel therapies for vitiligo [18].

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